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09/902,713	07/10/2001	Audrey Goddard	10466/71	1320

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EXAMINER	
KEMMERER, ELIZABETH	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/902,713	**Applicant(s)** GODDARD ET AL.	
	Examiner Elizabeth C. Kemmerer, Ph.D.	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 March 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *13 March 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *39-43*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: please see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

ATTACHMENT TO THE ADVISORY ACTION

Claims 39-43 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for reasons of record.

Claims 39-43 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record.

Applicant's arguments (received 13 March 2007) have been fully considered but are not found to be persuasive for the following reasons.

Applicant maintains their assertion that it is more likely than not that gene amplification results in overexpression of the protein. From p. 2 to p. 9 of the remarks received 22 August 2006, Applicant takes issue with Pennica et al., Konopka et al., Hu et al., LaBaer, Chen et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al. Applicant relies on Orntoft et al., Hyman et al., Pollack et al. and Futcher et al. as supporting their position. This has been fully considered but is not found to be persuasive. Hu et al. and Haynes et al. have already been discussed fully on the record. Pennica et al. and Konopka et al. constitute evidence that gene amplification is not predictive of increased mRNA levels. Applicant's criticism of Hu et al. and LaBaer for using faulty statistical analysis is not fatal to the rejection. Hu et al. and LaBaer were published in peer-reviewed journals, so it cannot be alleged that they

are scientifically deficient. Even if, *arguendo*, Hu et al.'s and LaBaer's statistical analysis was not sufficiently stringent, the instant application provides no statistical analysis, and thus Applicant is holding Hu et al. and LaBaer to a higher standard than their own disclosure. The arguments with regard to Chen et al. are duplicative of those of record; thus Chen et al. continues to be relied upon for reasons of record. Applicant quotes from Beer et al.; however, the quoted passage is relevant to whether or not oligonucleotide microarrays are predictive of mRNA levels *in situ,* and NOT whether gene amplification is predictive of increased mRNA, or is increased mRNA is predictive of increased polypeptide levels. Applicant's argument that Gygi et al. are focussed on accuracy and thus is not relevant is not persuasive because the reference clearly shows that protein levels cannot be predicted from mRNA levels. Applicant's arguments concerning Lian et al. and Fessler et al. are substantially duplicative of those of record and thus are not persuasive for reasons of record. Regarding Greenbaum et al., Applicant quotes from a passage that is relevant to highly expressed ORFs. There is no evidence that PRO269 is a highly expressed ORF. Greenbaum et al. establishes that polypeptide levels are controlled at several points and cautions against relying on mRNA levels to predict polypeptide levels.

At p. 9 of the response, Applicant takes issue with the examiner's statement that the specification has not identified anything rare. Applicant has taken the examiner's statement out of context. The statement was made in response to Applicant's argument that they are not required to establish overexpression in a majority of tumors, and that markers for rare tumors are valuable (see p. 2 of the remarks received 21 August 2006).

Beginning at p. 10 of the response, Applicant again reviews the declarations of Drs. Polakis, Goddard, and Scott as well as the Orntoft reference. As these have already been addressed extensively on the record, the examiner maintains that they are insufficient to overcome the rejections for reasons of record.

Beginning at p. 13 of the response. Applicant again relies on several references already of record: Alberts, Lewin, Meric, Celis, and Futcher et al. Applicant urges that the publications demonstrate a trend of correlation found across proteins in general, that mRNA/protein correlation exists. This has been fully considered but is not found to be persuasive for reasons of record. As discussed in the previous Office Action, all of these publications acknowledge that there are other levels of control of protein expression levels, and thus the skilled artisan would not have assumed that elevated mRNA levels, or gene amplification, would result in elevated protein levels without doing the experiments to determine protein levels.

Applicant takes issue with Nagaraja et al., arguing that since the expression levels of so many fewer proteins than transcripts were measured, Nagaraja did not examine the corresponding protein levels for many tested genes that displayed differential mRNA expression. Applicants' arguments have been fully considered but are not found to be persuasive. Nagaraja et al. characterize comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with

proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and vice versa" (see pg 2329, first column). The variability between the transcript profiles (mRNA) and proteomic profiles of Nagaraja et al. simply provide evidence that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Applicants are holding Nagaraja et al. to a higher standard than their own specification, which does not examine corresponding protein levels for the PRO genes that purportedly displayed mRNA overexpression.

Applicants argue at p. 17 of the response that the findings of Waghray et al. suggest that the lack of mRNA/protein correlation in the study are mostly due to technical limitations. Applicants conclude, taking these technical limitations into consideration, a skilled artisan would not recognize a lack of general correlation between altered mRNA levels and altered protein levels based on the results of this reference. Applicants' arguments have been fully considered but are not found to be persuasive. Waghray et al. indicate at pg 1337 (col 2) possible several reasons as to the lack of concordance between RNA and protein found in their study, including translational control, post-translational modifications, or changes in protein turnover due to DHT treatment (pg 1337, col 2, last paragraph). It is also noted that in the same paragraph at pg 1337, Waghray et al. teach that "[i]t follows from the above considerations that monitoring gene expression at both RNA and protein levels may provide complementary information that could not be ascertained by solely measuring RNA or protein". As discussed in the previous Office Action, Waghray et al. conclude

that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-1334, Table 4). Waghray et al. clearly state that, "[t]he change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract). Thus, based upon the teachings of Waghray et al., the skilled artisan would recognize the unpredictability in the art of predicting protein levels from rnRNA levels.

At pp. 17-18 of the response, Applicants assert that Sagynaliev drew conclusions based on a literature survey of gene expression data rather than experimental data and therefore the conclusions may not be generally applicable. Applicants reiterate that transcriptomics studies typically examine a much larger number of genes than the number of proteins examined in corresponding proteomics studies. Applicants submit that the fact that only 18% of differentially expressed genes were confirmed with proteomics only indicates that the proteins were not identified on 2D gels, not that the proteins are not differentially expressed. Applicants further point to Sagynaliev's teachings regarding the technical problems in finding matching proteomic and transcriptomic data. Applicants' arguments have been fully considered but are not found to be persuasive. The results described in Sagynaliev are based on a literature survey that selected large-scale or genome-wide transcriptomic and proteomic studies that reported the results of experimental data. Therefore, the results presented in Sagynaliev are based on a comparison of large sets of experimental data from previously reported studies. The Examiner does not dispute the technological limitations set forth in Sagynaliev regarding confirmation of differential expression in transcriptomic

studies by proteomic studies. However, it is noted that Sagynaliev does not support Applicants' contention that differential gene expression is generally reflected in differential protein expression. Instead, Sagynaliev et al. was simply cited by the Examiner to emphasize the unpredictability in the art of correlating mRNA levels and protein levels.

Beginning at p. 19 of the response, Applicant takes issue with Lilley et al., Wildsmith et al., and King et al. Specifically, Applicant argues that King et al. and Wildsmith et al. (cited by Examiner previously) never indicate that it is more likely than not that a general correlation between the mRNA and protein levels for a gene does not exist and thus, does not suffice to establish a *prima facie* showing of lack of utility. Applicant points out reports of successful examples of microarray applications in human disease study by Wildsmith et al. Applicant also urges that the King reference discusses numerous advantages of the microarray technology and cites pg 2287. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the state of the art, as evidenced through textbooks and review papers, clearly establishes that polypeptide levels cannot be accurately predicted from mRNA levels. As discussed in the previous Office Action, Wildsmith et al. disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pages 269-286, especially pg 283). King et al. teach that "it has been established that mRNA levels do not necessarily correlate with protein levels" (pg 2287, 2nd full paragraph). King et al. state that it has

been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (pg 2287, bottom of col 1 through the top of col 2; see also Bork et al., Genome Res 398-400, 2000, especially pg 398, bottom of col 3). The Examiner acknowledges that while Wildsmith et al. and King et al. discuss the advantages of microarray technology and its application for human disease study, both references are clear in that the microarray is a valuable tool for the study of the *genetic* basis of complex diseases. For example, King et al. teach that "[m]icroarrays make it possible to investigate differential gene expression in normal vs diseased tissue, in treated vs nontreated tissue, and in different stages during the natural course of a disease, all on a genomic scale" (pg 2287, col 2, first full paragraph). These two references do not teach using DNA microarrays to uncover patterns of *protein expression*. Thus, the state of the art supports the Examiner's assertion that DNA microarrays cannot accurately predict protein levels and that analysis of protein expression is required to identify a protein as a potential marker for cancer.

At p. 21 of the response, Applicant takes issue with Bork et al., urging that Bork should be put on the record officially. This has been done with this advisory action, as per Applicant's request. Applicant further urges that Bork validates the positive potential of microarray technology. This has been fully considered but is not found to be persuasive. Bork et al. clearly emphasize the limitations of such studies. See p. 398, col. 3, last paragraph, wherein it is stated, "...conclusions from these data are often stretched with regard to protein products."

At pp. 21-22 of the response, Applicant again takes issue with Haynes et al. Since this has been extensively discussed on the record, no further comment is made here, and the Haynes publication is seen as supporting the rejection for reasons of record.

At pp. 22-23, Applicant takes issue with the Madoz-Gurpide et al. publication. Specifically, Applicant argues that clearly proteomic techniques are useful to obtain information beyond the overexpression of the tested protein, which is the most critical information for diagnostic purpose. Applicant states that the PRO269 polypeptides can be used in cancer diagnosis without any knowledge regarding the function or cellular role of the polypeptides. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Madoz-Gurpide state that "numerous alterations may occur in proteins that are not reflected in changes at the RNA level" (pg 53, 2nd full paragraph). Madoz-Gurpide et al. continue to disclose that "[u]nlike DNA microarrays that provide one measure of gene expression, namely RNA levels, there is a need to implement protein microarray strategies that address the many different features of proteins including determination of their levels in biological sample, and determination of their selective interactions with other proteins, antibodies, drugs, or various small ligands" (pg 53, 3rd full paragraph). Applicant argues that this additional information may be useful in elucidating the biological function of the protein, but it is not required to establish utility as a marker for cancer. While the Examiner agrees with Applicant that proteomic techniques are useful to obtain information beyond overexpression of the tested protein, Applicant seems have overlooked the first part of that statement from

Madoz-Gurpide which indicates that "there is a need to implement protein microarray strategies that address the many different features of proteins including determination of their levels in biological samples" (pg 53, 3rd full paragraph). Clearly, Madoz-Gurpide et al. indicate that mRNA levels do not necessarily correlate to protein levels and that comparative analysis of protein expression in normal and cancer tissues should be performed to identify aberrantly expressed proteins that may represent novel markers (pg 54, 2nd full paragraph). Additionally, while Madoz-Gurpide et al. state that numerous published studies using DNA microarrays justify the use of this technology for uncovering patterns of *gene expression*, the reference does not state that the published studies using DNA microarrays uncover patterns of *protein expression*.

At pp. 23-24 of the response, Applicant addresses the Godbout publication. Specifically, Applicant argues that Godbout et al. is not the only publication addressing gene amplification, and points to Bea et al. Further, Applicant urges that the section relied upon by the examiner in Godbout et al. is based upon two references published in 1987 and 1992, whereas Applicant has cited 2002 publications supporting their position. This has been fully considered but is not found to be persuasive. It is noted that the instant application claims priority to 1997. Therefore, the publications from 2002 are not reflective of the state of the art at the time of the invention, which was sometime before 1997. Furthermore, Godbout et al. make a strong case. Specifically, Godbout et al. state, "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell.*"

Regarding Bea et al., the subject of this abstract is the BMI-1 gene, which encodes a protein that was already functionally characterized as being involved in cancer pathology. The researchers began with this knowledge and then looked at whether or not the mRNA was elevated and/or the gene was amplified in cancerous cells. The instant claims involve PRO269, whose function is not known to contribute to cancer pathology. As noted in several publications looking at genes in general whose functions were not known, such as Li et al., a general correlation between gene amplification, increased mRNA expression, and elevated protein levels cannot be assumed.

Finally, Applicant addresses the Li et al. publication at pp. 24-25, arguing that Li et al. set a threshold for significant gene amplification that was too low. applicant refers to supplemental information accompanying the Li article, which Applicant attached to the response. This has been fully considered but is not found to be persuasive. The source of the supplemental information is not clear and thus cannot be deemed persuasive on this point.

In conclusion, the preponderance of the totality of the evidence the rejections of the claims under 35 U.S.C. § 101 and § 112, first paragraph (utility, enablement, and written description) have been made and maintained in the previous ten Office Actions, including in the examiner's answer mailed 15 November 2005. Essentially, Applicant asserts that the PRO269 polypeptide is useful as a diagnostic marker for lung tumors. It is the Examiner's position that the present specification fails to disclose (1) the physiological significance of the PRO269 polypeptide or (2) what the correlation

between PRO269 genomic DNA levels, mRNA levels, and protein levels are or (3) the significance of any such correlation in lung tumors. The state of the art has been cited and discussed extensively. The preponderance of the totality of the evidence supports the rejections. It is the examiners opinion that the issue has been fully developed for review by the Board of Appeals and Interferences.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Elizabeth C. Kemmerer

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